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# fupl: unbound fraction in plasma

      # pKa: compound dissociation constant
      # Pow: octanol:water partition coefficient
      # Dplw: phospholipid:water distribution coefficient
      # alpha: Ratio of Distribution coefficient D of totally charged species and that of the
neutral form
      # KAPPACell2plasma: Ratio of D inside the cell to D in the plasma, as derived from the
different pHs and pKas
      # FPpl: protein fraction in plasma - from Gardner 1980

# This predicts the coefficient of tissue to FREE plasma fraction via Schmitt's method (2004):
predict_Ktissue2plasma <- function(fupl,
      pKa,
      Pow,
      tissuedata=NULL,
      averagetissue=NULL,
      pkdata=NULL,
      Dplw=NULL,
      alpha=0.001,
      KAPPACell2plasma=1.0,
      FPpl = 75/1000/1.025,
      tissuelist=NULL,
      species="Human",
      Davis.corrected=TRUE)
{
  if (is.null(tissuedata))
  {
    tissuedata <- read.xls("pkdata.xls",skip=1,stringsAsFactors=FALSE)[1:13,]
    colnames(tissuedata) <-
c("Tissue","Fcell","Fint","FWc","FLc","FPc","Fn_Lc","Fn_PLc","Fa_PLc","pH","Mouse Vol (L/kg)","Rat Vol
(L/kg)","Dog Vol (L/kg)","Human Vol (L/kg)","Mouse Flow (mL/min/kg)","Rat Flow (ml/min.kg)","Dog Flow
(mL/min/kg)","Human Flow (mL/min/kg)")
  }

  if(is.null(averagetissue))
  {
    averagetissue <- read.xls("pkdata.xls",skip=0,stringsAsFactors=FALSE,sheet=3)
  }
  tissuedata[tissuedata$Tissue=="Rest",2:10]<-averagetissue[averagetissue$X==species,2:10]

  if(is.null(pkdata))
  {
    pkdata <- read.xls("pkdata.xls",skip=0,stringsAsFactors=FALSE,sheet=2)
  }

  Ktissue2plasma <- list()
  vol <- list()
  flow <- list()

  # water fraction in plasma:
  FWpl <- 1 - FPpl
  # protein fraction in interstitium:
  FPint <- 0.37 * FPpl
  # water fraction in interstitium:
  FWint <- FWpl

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if (is.null(tissuelist))
{
  tissuelist <- as.list(tissuedata$Tissue)
  names(tissuelist) <- tissuedata$Tissue
}

all.tissues <- rep(FALSE,length(tissuedata$Tissue))
names(all.tissues) <- tissuedata$Tissue

for (this.lumped.tissue in c(names(tissuelist),"Red blood cells","cleanup"))
{
  if (this.lumped.tissue == "cleanup")
  {
    this.lumped.tissue <- "Rest"
    if (!("Rest" %in% names(vol)))
    {
      vol[[this.lumped.tissue]] <- 0
      flow[[this.lumped.tissue]] <- 0
      Ktissue2plasma[[this.lumped.tissue]] <- 0
    }
    these.lumped.tissues <- tissuedata$Tissue[!all.tissues]
  }
  else {
    if (this.lumped.tissue == "Red blood cells")
    {
      vol[[this.lumped.tissue]] <- NA
      flow[[this.lumped.tissue]] <- NA
      if (!all.tissues["Red blood cells"])
      {
        these.lumped.tissues <- "Red blood cells"
        Ktissue2plasma[[this.lumped.tissue]] <- 0
      } else these.lumped.tissues <- NULL
    } else {
      vol[[this.lumped.tissue]] <- 0
      flow[[this.lumped.tissue]] <- 0
      Ktissue2plasma[[this.lumped.tissue]] <- 0
      these.lumped.tissues <- tissuelist[this.lumped.tissue]
    }
  }
  for (this.tissue in these.lumped.tissues)
  {
    if (!(this.tissue %in% tissuedata$Tissue))
      stop(paste(this.tissue,"not in list",paste(tissuedata$Tissue)))
    if (all.tissues[[this.tissue]] & this.tissue != "Rest")
      stop(paste(this.tissue,"assigned to multiple lumped tissues"))

    all.tissues[[this.tissue]] <- TRUE
    this.row <- tissuedata$Tissue==this.tissue

    vol[[this.lumped.tissue]] <- vol[[this.lumped.tissue]] +
as.numeric(tissuedata[this.row,paste(species,"Vol (L/kg)",sep=" ")]))
    flow[[this.lumped.tissue]] <- flow[[this.lumped.tissue]] +
as.numeric(tissuedata[this.row,paste(species,"Flow (mL/min/kg)",sep=" ")]))

    Fcell <- as.numeric(tissuedata[this.row,"Fcell"])
    # interstitial volume fraction:

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Fint <- as.numeric(tissuedata[this.row,"Fint"])
if (is.na(Fint)) Fint <- 0

# water volume fraction:
FW <- Fcell * as.numeric(tissuedata[this.row,"FWc"])
# neutral lipid volume fraction:
Fn_L <- Fcell * as.numeric(tissuedata[this.row,"FLc"]) *
as.numeric(tissuedata[this.row,"Fn_Lc"])
if (is.na(Fn_L)) Fn_L <- 0
# neutral phospholipid volume fraction:
Fn_PL <- Fcell * as.numeric(tissuedata[this.row,"FLc"]) *
as.numeric(tissuedata[this.row,"Fn_PLc"])
if (is.na(Fn_PL)) Fn_PL <- 0
# acidic phospholipid volume fraction:
Fa_PL <- Fcell * as.numeric(tissuedata[this.row,"FLc"]) *
as.numeric(tissuedata[this.row,"Fa_PLc"])
if (is.na(Fa_PL)) Fa_PL <- 0
# protein volume fraction:
FP <- Fcell * as.numeric(tissuedata[this.row,"FPc"])

#
print(paste(this.tissue,"Fcell",Fcell,"Fint",Fint,"FW",FW,"Fn_L",Fn_L,"Fn_PL",Fn_PL,"Fa_PL",Fa_
PL,"FP",FP))

# tissue pH
pH <- as.numeric(tissuedata[this.row,"pH"])

# # plasma:protein partition coefficient
KPpl = 1/FPpl*(1/fupl-FWpl)

# neutral phospholipid:water parition cofficient:
if (is.null(Dplw))
{
  Kn_PL <- Pow
} else {
  Kn_PL <- Dplw
}

# Octonol:water distribution coefficient:
if (pH <= 7)
{
  Dow <- Pow*((1 - alpha)/(1+10^(pH-pKa)) + alpha)
} else {
  Dow <- Pow*((1-alpha)/(1+10^(pKa-pH)) + alpha)
}

# neutral lipid:water partition coefficient
Kn_L <- Dow

# protein:water partition coefficient:
KP <- 0.163 + 0.0221*Kn_PL

# acidic phospholipid:water partition coefficient:
if (pH <= 7)
{
  Ka_PL <- Kn_PL * (1/(1+10^(pH-pKa)) + 20*(1 - 1/(1+10^(pH-pKa))))
}

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    } else {
      Ka_PL <- Kn_PL * (1/(1+10^(pKa - pH) + 0.05*(1 - 1/(1 + 10^(pKa -
pH))))))
    }

    # unbound fraction in interstitium:
    fuint <- 1/(FWint + FPint/FPpl*(1/fupl - FWpl))

    # unbound fraction in cellular space:
    fucell <- 1/(FW + Kn_L*Fn_L+Kn_PL*Fn_PL+Ka_PL*Fa_PL+KP*FP)

    this.PC <- ((Fint/fuint + KAPPAcell2plasma*Fcell/fucell))*fupl

    if (Davis.corrected)
    {
      if (this.tissue=="Adipose") this.PC <- 0.46222*this.PC
      if (this.tissue=="Bone") this.PC <- this.PC + 0.55791
      if (this.tissue=="Gut") this.PC <- 0.49591*this.PC + 0.35056
      if (this.tissue=="Kidney") this.PC <- 0.63812*this.PC + 0.61411
      if (this.tissue=="Liver") this.PC <- this.PC + 0.37409
      if (this.tissue=="Lung") this.PC <- this.PC + 0.52108
      if (this.tissue=="Muscle") this.PC <- this.PC + 0.22873
      if (this.tissue=="Skin") this.PC <- 0.42136*this.PC
      if (this.tissue=="Testis") this.PC <- this.PC + 0.59415
      if (this.tissue=="Thymus") this.PC <- this.PC + 0.8962
    }

    this.PC <- this.PC/fupl

    if (this.tissue == "Red blood cells") Ktissue2plasma[[this.lumped.tissue]] <-
this.PC
      else Ktissue2plasma[[this.lumped.tissue]] <- Ktissue2plasma[[this.lumped.tissue]]
+ vol[[this.lumped.tissue]]*this.PC
    }
    if (this.lumped.tissue != "Red blood cells") Ktissue2plasma[[this.lumped.tissue]] <-
Ktissue2plasma[[this.lumped.tissue]]/vol[[this.lumped.tissue]]
  }

  return(list(Ktissue2plasma=Ktissue2plasma,vol=vol,flow=flow))
}

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